

Male reproductive system

2011

1 Prim. sex organ : testis

a Seminiferous tubules

Spermatogenesis

- Germ cells (Spermatogonia)
- Sertoli cells



b Interstitial cells of Leydig

Hormones
mainly testosterone
Contain lipid granules

2 Second. sex organs :

a A system of tubules and ducts : epididymis & vas.

6 cm
(store & mature sperms)

b Accessory glands

- Seminal vesicle 60% of semen. Fructose
- Prostate 30% of semen. Alkaline

Oxytocin is needed for prostatic function.

PSA hydrolyse sperm motility inhibitor

- Cowper's gland 5% Mucus

c Penis

N.B Spermatic a. in contact with pampiniform plexus of spermatic v.

Sertoli cells

Blood testis barrier is the tight junction of Sertoli cells

a Keeps composition of Seminiferous tubular fluid.

Formed by Sertoli cells. It differs from plasma:

- More K^+ , androgen & estrogen
- Less Pln & glucose

b Prevents antigenic products of spermatogenesis to pass to blood $\rightarrow$ immune response.

c Prevents toxic and noxious agent from blood to pass to tubular fluid

Functions of Sertoli cells

1 Nourishing and protective role

For sperms

Nutrient is Glycogen

2 Phagocytic role engulf residual debris of spermatogenesis

(1)

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3 Formation of blood-testis barrier discuss

4 Secreting role

a Hormones

- Androgen binding pln ABP
- Mullerian inhibiting substance MIS
- Activins ++ FSH
- Inhibin FSH
- Estrogen

b Aromatase enzyme convert androgen to estrogen

c Proteolytic enzymes dissolve tight junction

d Tubular fluid rich in K^+ Discuss

Spermatogenesis

4 phases each takes 16 days
i.e. new set of spermatogonia every 16 days

1 Proliferative

1 prim. spermatogonia mitosis → 16 second. spermatogonia

2 Growth

1 second. spermatogonia → prim. spermatocyte

3 Maturation

a 1 prim. spermatocyte MEIOSIS → 2 second. spermatocytes
Diploid number of chromosomes Haploid

b 1 second spermatocyte mitosis → 2 (daughter spermatids)

4 Transformation spermiogenesis

1 spermatid → spermatozoa

Spermiation

Extrusion & maturation of immobile spermatozoa from Sertoli cells → mobile sperm in epididymis

Aided by

- | | | |
|------------------------------|---|---------------------|
| 1 <u>Myoepithelial cells</u> | : | Contractility |
| 2 <u>Sertoli cells</u> | : | Proteolytic enzymes |
| 3 <u>Prostate</u> | : | Relaxin hormone |

②

Male reproductive system

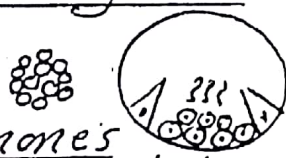
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Aided by Forward motility hormone FTH

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Contractility

2 Sertoli cells :

Proteolytic enzymes

3 Prostate :

Relaxin hormone

②

Sperm capacitation

Time needed by spermatozoa in $\varnothing$ tract (7 hours) to acquire the capacity to fertilize the ova

- ++ motility of sperm.
- prepared for acrosomal reaction

Acrosome is a cap (lysosome like organelle) which covers the sperm head & helps the penetration of the ovum.

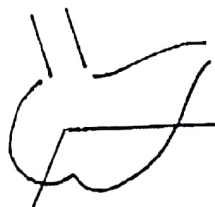
Facilitatory & not obligatory as fertilization occurs in vitro

Factors affecting spermatogenesis $8 < 5$

Hormonal Factors:

[1] LH

early stages
secrete testosterone



[2] FSH

Late stages

- ++ ABP
- ++ LH receptors on Leydig cells

[3] Testosterone

Maturation phase
early stages are androgen independent
Complete meiosis
Germinal epith
Develop. & Function

N.B. High conc. is caused by:

- 1 Local secretion by Leydig cells
- 2 ABP
- 3 Counter current bl. supply

[5] Other hormones

- 1 GH & prolactin early stages
- 2 Thyroxine
- 3 Leptin puberty
- 4 Estrogen in small amount mediate action of FSH

[4] Activins ++ FSH
Inhibin -- FSH

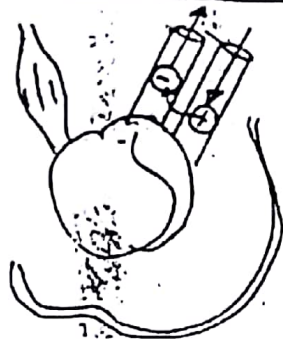
Other factors

6 Temperature

Optimum temp. 32°C

(+) temp

Cremasteric ms
Dartos ms



(-) temp

thin skin & no SC fat
counter current system
of testicular vessels

Prove

Cryptorchidism

- sterility if bilateral
- Testosterone & second sex organs are normal

Prolonged fever, hot baths & tight underpants

- inhibits spermatogenesis

7 Diet Ptn

Vitamins: A, B, C & E

8 a Prolonged exposure to X ray & radiation

b Bacterial, chemical toxins

c Hypoxia

Inhibit spermatogenesis.

Testosterone

Steroid hormone

- 90% of testicular androgens

- Sources
 - ♂ interstitial cells of Leydig stim. LH
 - ♀ granulosa cells of follicles stim. LH
 - ♀ aromatase → estrogen
 - ♀ adrenal cortex stimulus ACTH

- Secretion adult ♂ 4-9 mg/day

- plasma level ♂ 300-1000 ng/dl
- adult ♀ 30-70 ng/dl

(4)

- Transport 98% bound to ptn 2% free
- Fate Most amount $\longrightarrow$ 17 ketosteroids
Small " $\longrightarrow$ estrogen
Conjugated with glucuronic acid in 
- Mode of action Genomic action
Testosterone $\xrightarrow{5\alpha \text{ reductase}}$ dihydrotestosterone (DHT)
-- σ eunuchoidism
Less active More active hormone
10% level of testosterone
Fetus Internal genitalia Fetus External genitalia
Adult Bones & muscles Adult Skin, penis, prostate

• Control of secretion

1 Intrauterine life.

Sex differentiation
7th week

A Development of gonads

Origin Bipotential primordial gonads

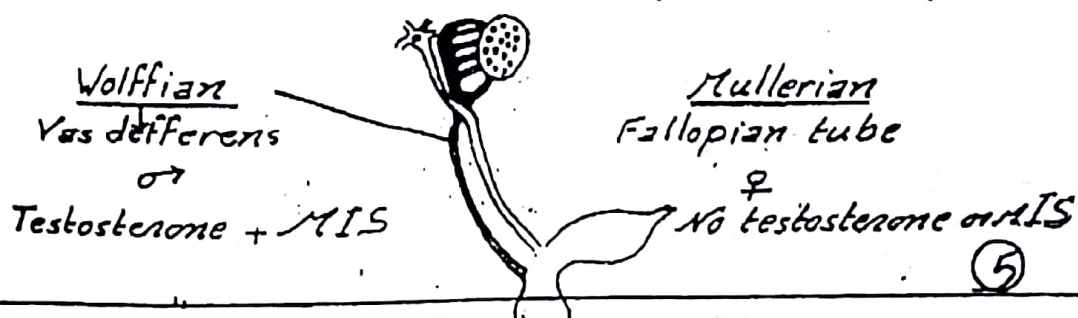
Control absence or presence of Sex determining region of Y chromosome.



B Development of ducts

Origin Wolffian and Mullerian ducts

Control Testosterone and Mullerian inhibiting substance (of Sertoli cell)



2 neonatal period Testosterone secretion stops
Due to -- GnRH & -- LH

3 puberty Testosterone is secreted
In response to GnRH & LH

4 After 60 years Testosterone secretion declines

Functions of testosterone

A Intrauterine life: 3 Ds page 7

B Puberty and adulthood:

Musculining effect

- 1 Primary sex organ (testes)
Spermatogenesis ←
- 2 Secondary sex organs (accessory)
 - a Seminal vesicles, prostate, bulbourethral glands (testosterone)
 - b Penis & scrotum (DHT)
- 3 Secondary sex characters

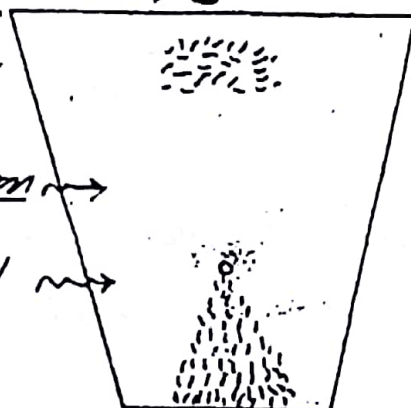
- Hair :

- Skin : acne

- Larynx → low pitch

- Body configuration →

- Behavioural effects →



General metabolic effects

- 1 Ptn anabolic (very high)
muscle - Bone - genitalia
- 2 Secondary to ptn anabolic
- salt & H₂O retention
- growth spurt then epiphyseal closure
- 3 ++ kidney size

-- scalp hair
++ body hair
++ pubic hair Δ
++ sebaceous g secretion
enlarges larynx low pitch
cords thick long
voice deep

broad shoulder
narrow pelvis
muscles enlarge

++ libido
aggression

⑦

Intrauterine actions of testosterone: 3 Ds

1 Development of:

- Wolffian duct to epididymis, vas deferens & seminal vesic.
- Urogenital sinus & tubercle to prostate penis & (DHT)
- Inhibition of ♀ ext. genitalia (DHT)

2 Differentiation of male brain ♂

- Gonadotropin secretion is continuous not cyclic [♀]
- Aggression. ^{independent cycle}

3 Descent of testicle in scrotum (DHT)

Note

Inhibin

-- FSH In ovary, -- androgen → -- estrogen
 2 forms α & β In plasma, both binds to α_2 globulin
 2 subunits α & β polypeptides
 Origin ♂ testis (Sertoli cell)
 ♀ antral fluid of ovarian follicles

Activins

++ FSH
 Heterodimers BA B β (mesoderm)
 Receptors are found in embryo, gonads, brain
 In tissues, activin binds to follistatin (glycoprotein) → inactivation

Erection

Vascular phenomenon: Arteries VD & Veins are compressed
Started by parasymp. stim. pelvic nerve (nervi erigentes)
 - cholinergic fibres → VIP is co-transmitter
 - non cholinergic fibres → ++ NO → ++ cGMP → VD
Terminated by symp. stim. Viagra ↑ cGMP

Ejaculation

Emission Movement of semen into urethra

Mediated by symp. stim. ^{symp. thal}

Ejaculation proper Propulsion of semen out of urethra

Mediated by reflex cont. of bulbocavernosus muscle.
 Somatic

Abnormal testicular function

1 Crypt orchidism undescended testis

10% newly born 2% 1 y 0.3% puberty

- Effects - Sterility if bilateral
 - Normal testosterone i.e. normal σ character
 - High incidence of cancer testis

Descent of testis depends on MIS &

Testosterone i.e. DHT

It Before puberty i.e. before degeneration of spermatogenesis

- Gonadotropins
- Surgical.

2 Hypogonadism

(a) prim Complete e.g. Castration (b) second Pituitary
Partial e.g. Cryptorchidism gonadotropin hypoth

Eunuchoidism - Leydig cell deficiency in childhood.

<u>Castration</u>	<u>Before puberty</u>	<u>After puberty</u>
1 <u>Target organs</u>		
- <u>prim. sex. organ</u>	Sterility	Sterility
- <u>second. sex. organs</u>	Remain infantile	Little regression
- <u>second. sex. characters</u>	like ♀ $\leftarrow$ voice hair narrow shoulder	Regress slowly
2 <u>Bones</u>	Tall stature	Osteoporosis
3 <u>Others</u>	Weak muscles	Hot flushes, irritable no libido & depressed.

3 Congenital deficiency of 5 α reductase

Type 1: 5 α reductase present in skin & scalp.

Type 2: 5 α reductase " Genital skin & Genital tissues
 prostate

Cause Gene mutation of Type 2 5 α reductase

Effects σ pseudo her rodit. (discuss)

Puberty

Definition

1 Men

4 Thel

2 Pub

3 Adren

arch

Gonads Gonadotropins → Reproduction

1st menstrual cycle

Development of breast

Development of pubic hair

++ adrenal androgen (Cortisol & ACTH)

due to change in enzyme system and m androgen start hormone. ACTH

Growth spurt of 11-12y ends at 13½

Causes of onset of puberty

1. Genetic

2. Correlation between mother & daughter menarche (loose)

3. Geographic location & exposure to light light increases testis

4. State of nutrition

5. Body composition & Fat deposition leptin

Heavy exercise Marked obesity (- leptin) & anorexia → Delay

Control of onset of puberty

Stoppage of inhibition which prevents pulsatile release of GnRH in children.

Abnormal puberty

Precocious

True

early development of second sex characters

With gametogenesis

++ GnRH due to Cause

1 Constitutional

2 Post hypoth tumour

3 Pineal body tumour

4 Gonadotropin independent

++ LH receptors sensitivity

Pseudo

No gametogenesis

++ Sex hormones due to:

1 Gonadal tumour Leydig cells
Granulosa cell

2 Adrenal tumour
secreting androgen or estrogen

Just ↑ testosterone
that -ve feedback mechanism and GnRH ↓

Delayed puberty

Eunuchoidism

20y

Prim. Amenorrhoea

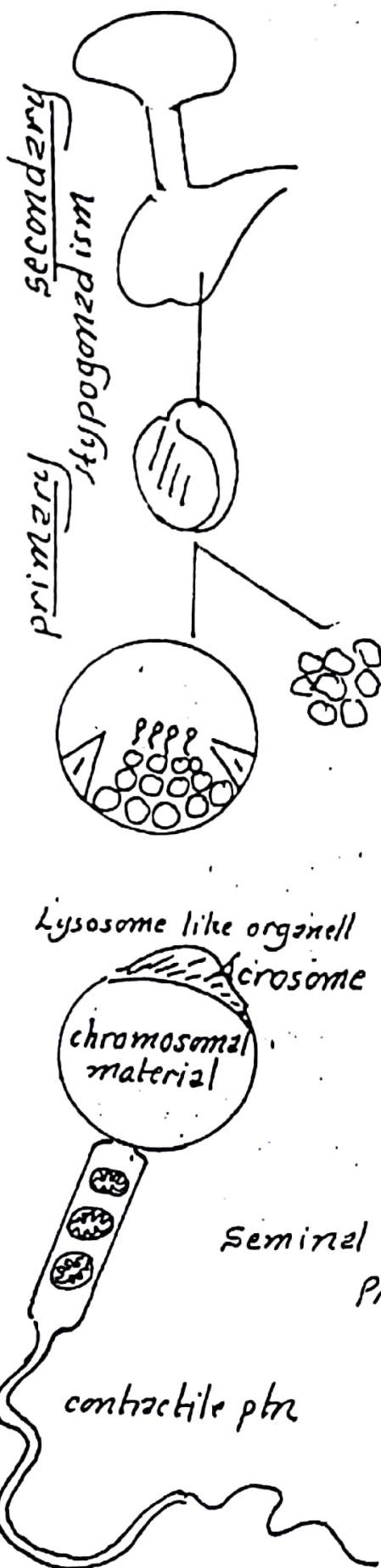
17y

Partial hypopituitarism

Turner's syndrome

9

Testicular function tests



1 Urinary gonadotropins

- prim. hypogonadism ++
- second hypogonadism --

2 Urinary 17 ketosteroids

- Sterite $\sigma \rightarrow$
- = impaired Leydig cell
 - normal = " gametogenic function

3 Testosterone, FSH, LH in blood

(Semenal LH ptn)

- | | Testosterone | FSH & LH |
|-----------------|--------------|----------|
| - <u>prim.</u> | -- | ++ |
| - <u>second</u> | -- | -- |

4 Semen analysis

① Volume 2-4 ml / ejaculation

② Number 80-100 million / ml
 below 50 " subfertile
 below 20 " infertile
 obstruction σ 0 azoospermia

③ Sp. gr 1028 ++ $\rightarrow$ ++ viscosity
 $\rightarrow$ -- motility

④ Motility 60% actively motile
 3 mm / min. after 6 hours

Seminal vesicle ⑤ Fructose 150-650 mg %

Prostate ⑥ pH 7.3 7.5

⑦ sperm quality > 25% abnormal shapes

⑧ Colour white opalescent

5 Testicular biopsy

Seminiferous tubules

- sperm : obstruction
- no sperm : no gametogenic function

(10)

gynecomastia development of breast in σ
usually bilateral but may be unilateral

Physiological causes

- 1 Newly born: transplacental passage of maternal estrogen
- 2 70% of normal boys at puberty
- 3 in men after 50 y testosterone (androgen)

Pathological causes

- 1 Complication of estrogen therapy
 - 2 Pt with estrogen secreting tumours
 - 3 Liver cirrhosis
 - 4 Digitalis therapy (weak estrogenic)
- Laboratory ++ estrogen/androgen ratio

Factors affecting spermatogenesis

Hormonal , Temp & Physical Factors

Notes :

- 1 Head of the sperm has olfactory receptors
- 2 Ability of sperm to move forward (progressive motility) depends on activation of a ptn called cat-sper (CAT sperm) which is a Ca^{++} ion channel that permits cAMP generated Ca^{++} influx.
- 3 Sperm membrane contains germinal angiotensin converting enzyme with unknown function

MALE REPRODUCTIVE SYSTEM

Male sex organs:

- 1- Primary sex organ (testis).
- 2- Secondary internal sex organs:
 - a- Ducts; epididymis & vas deferens. (*store & mature sperms*)
 - b- Accessory sex glands; seminal vesicles, prostate & the bulbourethral (Cowper's) glands.
- 3- External copulatory organ (penis).

Testis has 2 main functions:

- 1- Spermatogenesis.
- 2- Production of steroid hormones mainly testosterone.

Semineferous tubules have 2 types of cells:

- 1- Spermatogonia (primitive germ cells) that produce spermatozoa (spermatogenesis).
- 2- Sertoli cells which are large cells with a multilobed nucleus & a large amount of cytoplasm rich in glycogen.
They have vital rôle in spermatogenesis.
The tight junctions between Sertoli cells form the blood brain barrier.

Interstitial cells of Leydig contain lipid granule & secrete testosterone.

Blood supply of the testis:

The spermatic arteries to the pampiniform plexus of the spermatic veins. This arrangement permits counter current exchange of heat & testosterone between the arteries & the plexus.

SPERMATOGENESIS

- 1- The primary spermatogonia dividing mitotically to produce secondary spermatogonia.
- 2- The secondary spermatogonia increase in size to form primary spermatocytes, which divide meiotically to produce secondary spermatocytes, each carrying half the number of chromosomes (22 X or 22 Y i.e. haploid number).
- 3- The secondary spermatocytes undergo a second stage of meiosis to form daughter **spermatide**
N.B. Each successive division during spermatogenesis moves the germ cells towards the center of the semineferous tubule, so that the spermatids are closest to the lumen.

4- The spermatids are converted without further cell division into spermatozoa.

4 stages of spermatogenesis take 64 days.

These stages are equally spaced in time, which means that new sets of spermatozoa arrive in the tubule lumen every 16 days.

SPERMATION:

- It is the process of completing maturation of the immobile spermatozoa, which are present in the tubular fluid to mature mobile sperms (rich in cAMP content & forward motility hormone FMH) in the epididymis.

-Spermiation is aided by:

- 1- Contractility of myoepithelial cells lining the seminiferous tubules.
- 2- Proteolytic enzymes released from the Sertoli cells.
- 3- Relaxin secreted by the prostate.

BLOOD- TESTIS BARRIER

- It is the tight junctions between adjacent Sertoli cells.
- It prevents the passage of certain molecules from the interstitial tissue & basal compartment (part of the tubule near basal lamina) to reach the tubular lumen (adluminal compartment) & vice versa.

These molecules include:

- 1- Antigenic products resulting from spermatogenesis are forbidden from entering the blood thus preventing an autoimmune response.
- 2- Any harmful blood-borne noxious agents are prevented from reaching the tubular lumen & destroying the germ cells.

However, steroids & maturing germ cells pass through this barrier.

TUBULAR FLUID:

- It is the fluid in the lumen of the seminiferous tubules.
- The Sertoli cells form it.
- It is different from the plasma because of the blood- testis barrier i.e. it contains very little protein & glucose, but it is rich in androgens, estrogens, K, inositol, glutamic & aspartic acids.

Estrogen helps the reabsorption of water content of fluid **concentrating the spermatozoa** in a small amount of fluid, which is vital for the fertility of the spermatozoa.

FUNCTIONS OF SERTOLI CELLS:

- 1- Nourishing & protective role for sperms: nutrient is glycogen.
- 2- Phagocytic role: engulfing any residual debris remaining from spermatogenesis.
- 3- Secreting role; hormones:
 - a- Androgen binding protein (ABP); which maintains a high & stable supply of androgens in the tubular fluid.
 - b- Activins; which stimulate the FSH secretion.
 - c- Inhibin; which inhibits the FSH secretion.
 - d- Mullerian inhibitory substance (MIS), which causes regression of the Mullerian duct in the male foetus during the intra-uterine life.
 - e- Esterogens.

Sertoli cells also secrete:

- a- Aromatase enzyme which converts androgens to estrogens.
- b- Proteolytic enzymes for the dissolution of tight junctions thus helping in the progress of the developing germ cells to move towards the lumen.
- c- Tubular fluid rich in K⁺
- 4- Formation of blood- testis barrier (discuss).

FACTORS AFFECTING SPERMATOGENESIS:

HORMONAL FACTORS:

1- Luteinizing hormone (LH) → ++ androgens that stimulate spermatogenesis.

2- Follicle stimulating hormone (FSH):

- Acts on Sertoli cells to facilitate the late stages of spermatid maturation.
- +++ the production of androgen binding protein (ABP).
- Sensitizes the cells of Leydig to the LH action.

3- Androgens through acting on Sertoli cells are essential for:

- Spermatogenesis i.e. maturation of spermatids to spermatozoa, although the earlier stages are androgen independent.
 - Development & maintenance of the germinal epithelium.
 - Complete meiosis.
- Earlier stages of spermatogenesis are androgen independent*

Testosterone is kept in high concentrations locally via:

- a- Production of high amounts by the cells of Leydig.
- b- Presence of androgen binding protein.

c- Presence of counter current mechanism.

4- Inhibin & activins which regulate the secretion of FSH by anterior pituitary.

5- Other hormones:

- **Thyroxine**; myxedema is associated with inhibition of spermatogenesis & infertility.
- **Growth hormone & prolactin** are important for early division of spermatogonia.
- **Leptin** has a role in the onset of puberty & the start of spermatogenesis.
- **Estrogens in small amounts** mediate the action of FSH.

OTHER FACTORS:

6- Temperature:

The temperature of the testicles is kept near their optimum temperature 32°C through the following factors:

- a- **Thin skin & no subcutaneous fat** in the scrotal sac.
- b- Tonic contractions of **dartos muscle** in cold weather to pull the testis to the warmth of the trunk.

Note: prolonged fevers, hot baths at temperature above 40° for 30 minutes or tight underpants may affect the seminiferous tubules & inhibit spermatogenesis.

7- Diet:

A balanced diet includes vitamins A, B, C & E, which are vital for spermatogenesis.

8- Other factors:

- **Prolonged exposure to X-ray or irradiation** cause irreversible damage of the seminiferous tubules, although the cells of Leydig maintain its secretion of testosterone.
- **Bacterial, chemical toxins & O₂ lack** depresses spermatogenesis.

SECONDARY SEX ORGANS

A) System of tubules & ducts:

- 1- **Epididymis**: single 6 cm long coiled duct, where storage & maturation of spermatozoa are completed.
- 2- **Vas deferens**: muscular duct, which contracts to propel the spermatozoa to the prostate.

B) Group of accessory glands: secrete seminal plasma

1- Seminal vesicle: 60 % of the seminal plasma

It produces a fructose rich secretion, fructose is the fuel for the sperms.

It also contains ascorbic acid, ergothionine, flavins & prostaglandins.

Fructose in semen 1.5 - 8.5 mg/ml

2- Prostate:

It secretes alkaline fluid rich in phospholipids, cholesterol, Ca^{++} & proteolytic enzymes as phosphatase, fibrinolysin & fibrinogenase.

Oxytocin is required for normal prostatic development & function.

The prostate also produces prostate-specific antigen (PSA) in the semen & blood. PSA hydrolyses the sperm motility inhibitor.

Increased plasma PSA is observed in prostatitis & in benign or malignant prostatic tumors.

3- Cowper's glands:

They secrete mucus, which neutralizes the acidity of the urethra.

MECHANISM OF ERECTION:

The penis contains erectile tissues, which consist of cavernous venous sinuses bound by fibro-elastic tissue.

During sexual intercourse, the arteries become dilated.

Meanwhile, the veins that drain the sinuses are compressed & prevent blood from leaving.

Factors mediating erection:

Parasympathetic fibres in pelvic nerve (nervi erigentis) produce vasodilatation of penile arteries.

1- Cholinergic fibres; VIP is secreted as cotransmitter.

2- Noradrenergic fibres, which secrete nitric oxide synthase to catalyze synthesis of nitric oxide (NO) $\longrightarrow$ $++$ cGMP, which is a potent vasodilator.

Normally, erection is terminated by sympathetic vasoconstrictor impulses.

EJACULATION:

Ejaculation is a spinal reflex composed of 2 parts:

a- Emission: it is the movement of semen into the urethra.

It is caused by contraction of smooth muscles of vas deferens & seminal vesicle.

It is mediated by sympathetic fibres.

b- Ejaculation proper: propulsion of the semen out of the urethra.

It is caused by contraction of **bulbocavernosus muscle**.

The reflex is stimulated by touch receptors in the glans penis to reach the spinal cord through the internal pudendal nerves.

CAPACITATION:

- It is the ability of the spermatozoa to produce fertilization.
- It involves 2 components, which occurs **after 7 hours in the female genital tract**:

- a- Increased motility of the sperms.

- b- Facilitating the preparation of sperms for acrosomal reaction.

Capacitation is Facilitatory (not obligatory) for fertilization (can occur in-vitro)

CHARACTERISTICS OF THE SPERM:

- A mature sperm is a motile cell, rich in DNA.

- It is formed of:

- a- **Head**: made up mostly of **chromosomal material**.

Acrosome is a cap covering the head & is a lysosome- like organelle rich in enzymes involved in sperm penetration of the ovum.

- b- A **motile tail**, with the proximal portion covered by a **sheath** rich in **mitochondria**.

SEMEN

Characters of the semen:

1- **Volume**: 2-4 ml / ejaculation.

Decreased volume & fructose content reduces fertility.

2- **Sperm count**: 80 – 100 millions/ ml.

Oligospermia: is a low sperm count below 50 millions / ml

A count below 20 millions causes infertility.

Azospermia: absence of sperms in the semen.

3- **Specific gravity**: 1028.

Increased viscosity depresses the motility of sperms, thus decreasing fertility.

4- **Sperm motility**: 60 % of the total sperms should be actively motile to ensure fertility.

5- **pH**: 7.3 to 7.5

6- **Sperm quality**: large number of abnormal forms of sperms (double-headed, double-tailed, coiled, short-tailed) is associated with infertility.

7- Colour is white & opalescent.

MALE HORMONES

TESTOSTERONE

*Testosterone is the principal hormone (90 %) of the testicular androgens.

It is a steroid hormone secreted from:

- a- Interstitial cells of Leydig in the testis stimulated by LH.
- b- Adrenal cortex stimulated by ACTH.
- c- In granulosa cells of the growing follicles, to be converted by aromatase to estrogen.

***Precursor molecules:**

- 1- Cholesterol in the Leydig cells.
- 2- Androstenedione in adrenal cortex.

***Secretion:**

The rate of testosterone secretion is 4- 9 mg / day in normal adult males. It is about 300 – 1000 ng / dl in adult males & 30 – 70 ng / dl in adult females.

***Transport of testosterone in plasma:**

- 98% of testosterone is bound to protein in plasma:
65% to gonadal steroid binding protein (GBG) & 33% to albumin.
- 2% is free.

***Fate of testosterone:**

- Most of the testosterone is converted to 17 – ketosteroids to be excreted in urine.
- A small amount is converted to estrogen by aromatization.
- Conjugation with glucuronic acid & sulphates in the liver.

***Mode of testosterone action:**

- Genomic action.
- Testosterone can be converted to dihydrotestosterone (DHT) by 5 alpha reductase in some target cells.

***Significance of DHT:**

- 1- It circulates in plasma at a level of 10 % that of testosterone & binds to the same receptors of testosterone forming more stable hormone- receptor complexes than testosterone.

2- It amplifies the action of testosterone in target tissues.

***Control of testosterone secretion:**

A) IN INTRAUTERINE LIFE: SEX DIFFERENTIATION

1- Development of testicles (male primary sex organs):

The bipotential gonads at 7th – 8th week differentiates into testicles, under the effect of a substance from the sex – determining region of Y chromosome (SRY). The embryonic testis secretes testosterone.

2- Development of male secondary sex organs:

- a- Sertoli cells secrete Mullerian inhibiting hormone (glycoprotein), which causes regression of Mullerian duct i.e. embryonic female reproductive tract.
 - b- Leydig cells secrete testosterone (steroid), which stimulate Wolffian duct to differentiate into male internal genitalia (epididymis, vas deferens, seminal vesicles & prostate).
- Also, testosterone stimulates formation of penis & scrotum.

B) DURING NEONATAL PERIOD TILL PUBERTY:

The secretion of testosterone stops due to --- GnRH & LH.

C) AT PUBERTY:

Testosterone is secreted in response to hypothalamic GnRH & pituitary LH. Then, it declines after the age of 60 years.
There is negative feedback between testosterone & GnRH and LH.

***FUNCTIONS OF TESTOSTERONE:**

A) DURING INTRAUTERINE LIFE:

Testosterone is responsible for 3D:

1- Differentiation of male brain:

- a- Male pattern of sexual behavior (aggressiveness).
- b- Male pattern of hypothalamic control of gonadotrophic secretion.

2- Development of:

- a- Wolffian duct into epididymis, vas deferens & seminal vesicle.
- b- Urogenital sinus into prostate, urethra & scrotum.
- c- External male genitalia & inhibiting those of the female by the action of DHT – receptor complexes.

3- Descent of the testicles in the scrotum by the action of DHT.

AT PUBERTY & DURING ADULTHOOD:

1- MUSCULINIZING EFFECTS:

a- On the primary sex organ:

Testosterone is essential for spermatogenesis.

b- On the secondary sex organs:

The seminal vesicle, prostate & Cowper's glands are largely dependent on testosterone for their growth & functions.

Also, the external genitalia is absolutely dependent on DHT for their development & growth.

c- Secondary sex characteristics:

- **Hair:** body hair is increased & scalp hair is decreased.

Hairline is indented (recedes back) in the lateral frontal region.

Hereditary baldness appears.

Pubic hair is triangular with apex up towards the umbilicus.

- **Skin** is thickened with ++ sebaceous gland secretion causing acne.

- **Voice:** larynx enlarges, vocal cords increase in length & thickness.

So, voice becomes deep & lower in pitch.

- **Body configuration:** shoulders broaden & muscles enlarge.

- **Behavioral changes:** ++ libido (sexual desire) & more aggression.

2- ANABOLIC EFFECTS:

- a- ++ protein synthesis in sex organs, muscles & bone. In addition, it causes increase in the growth spurt (rate of growth).

- b- Moderate retention of sodium, potassium, water, sulphates & phosphates.

- c- *Testosterone increases kidney size.*

INHIBIN

- 2 forms; inhibin A & inhibin B

- It is protein, which inhibits FSH secretion.

- **Origin:**

It is secreted from Sertoli cells in males & granulosa cells in females

- **Inhibin is formed of 2 polypeptide units α and β .**

Inhibin A is composed of $\alpha \beta_A$ subunits & inhibin B is composed of $\alpha \beta_B$ subunits.

- Inhibin especially **inhibin B** directly acts on the pituitary to inhibit FSH.

- It has intra-ovarian action as it decreases androgen production & thus estrogen formation

ACTIVINS

- They are heterodimers formed of the subunits α , β_A , β_B (β_A , β_A , β_B , β_B).
- They stimulate FSH secretion.
- There are 2 types of activin receptors, which are serine kinases.
- The receptors are found in:
 - a- Embryo: involved in mesodermal formation.
 - b- Gonads.
 - c- Brain.
 - d- Bone marrow: some activins are involved in white blood cell development.
- In plasma, α_2 - macroglobulin is found to bind to activins & inhibin.
- In tissues, activins bind to follistatins (glycoproteins) to inactivate the biologically active activins. However, follistatins' relation to inhibin is still unsettled.

TESTICULAR FUNCTION TESTS

1) Semen analysis: see before.

2) Estimation of urinary gonadotrophins:

- In primary hypogonadism: gonadotrophins are high (no feedback).
i.e. hypergonadotrophic hypogonadism.
- In secondary hypogonadism: gonadotrophins are low (the pituitary is non- functioning) i.e. hypogonadotrophic hypogonadism.

3) Estimation of natural 17- ketosteroids:

- They decrease in impaired Leydig cell function.
- A sterile male with normal 17- ketosteroids level indicates absence of gametogenic activity.

4) Estimation of blood testosterone level, FSH & LH:

- A decrease in testosterone & gonadotrophins (FSH & LH) blood levels denote secondary hypogonadism to pituitary or hypothalamic causes.
- A decrease in testosterone with a high gonadotrophin level denotes primary hypogonadism.

5) Testicular biopsy:

A sample of testicular tissue is examined histologically.

- If the seminiferous tubules contain sperms, this denotes duct obstruction.
- If the seminiferous tubules contain no sperms, this denotes absence of gametogenic activity.

ABNORMALITIES OF TESTICULAR FUNCTION:

1) CRYPTORCHIDISM:

- It is failure of testicular descent in the scrotum during fetal development.
- It occurs in 10 % of newly born males. It falls to 2 % by the age of one year & 0.3% at puberty.
- Descent of testis in scrotum depends mainly on MIS & testosterone.
- **Treatment:**
 - a- Gonadotrophic hormones.
 - b- Surgical treatment.
- **Side effects of cryptorchidism:**
 - a- Higher incidence of malignant tumours in undescended testis.
 - b- Irreversible damage to spermatogenic epithelium of testis due to higher temperature in the abdomen.

2) MALE HYPOGONADISM:

- It depends upon whether testicular deficiency develops before or after puberty.
- **Causes of hypogonadism:**
 - i- **Primary:** local disease in testis or surgical castration.
 - ii- **Secondary:** disorder in hypothalamic – hypophyseal axis.

a) Before puberty:

The clinical picture due to Leydig cell deficiency in childhood is called **eunuchoidism**.

The eunuchoid individuals have the following characters:

- 1- **Tall stature** due to delayed union of epiphysis till 20 years.
- 2- **Configuration similar to an adult female** i.e. like hair distribution, narrow shoulder, small muscles & small larynx (high pitched voice).
- 3- **Small genitalia.**

b) After puberty:

The secondary sex characters regress slowly since they need little for their maintenance.

If it is secondary to castration, it leads to loss of libido, hot flushes, depression & irritability.

3) CONGENITAL 5 ALPHA REDUCTASE DEFICIENCY:

- Cause: gene mutation of type 2, 5 alpha reductase.
- 5 alpha reductase is an enzyme needed for the conversion of testosterone to DHT.

Type 1: 5 alpha reductase present in body skin & scalp

Type 2: 5 alpha reductase present in genital skin, prostate & other genital tissues.

- Effect: *Pseudohermaphroditism (discuss)*

PUBERTY (ADOLESCENCE)

- It is the period in which there is activation of gonads of both sexes by the gonadotrophins to the point where reproduction is possible.

- In females, the puberty takes place through the following events;

- 1- **Thelarche:** development of breasts.
- 2- **Pubarche:** development of axillary & pubic hair.
- 3- **Menarche:** start of the first menstrual period.
- 4- **Growth spurt:**

It is the linear growth velocity in cm/ year

In females, it starts at the age of 11- 12 years & ends at 13 ½

In males, it starts 1- 1 ½ years later

5- In males & females, **adrenarche** is an increase in the secretion of adrenal androgens. It occurs without any change in the secretion of ACTH or cortisol.

Causes of adrenarche:

- 1- Change in the enzyme systems in the adrenal, so that more pregnanolone is diverted to androgen pathway.
- 2- Increased secretion of a newly identified adrenal androgen stimulating hormone (ASH) from the anterior pituitary. This hormone acts on adrenal cortex to increase the adrenal androgen.

Causes of onset of puberty:

- 1- Genetic factors
- 2- State of nutrition
- 3- Loose correlation between the of menarche in mother & daughter
- 4- Body composition & fat deposition:
Anorexia, heavy exercise, severe obesity & decreased leptin secretion
→ delayed menarche
- 5- Geographic location & exposure to light:

Distance from the equator & lower altitudes are associated with early onset of puberty.

Control of the onset of puberty:

In children, GnRH can not be secreted in pulsatile manner; a neural mechanism may exist which operates to inhibit the pulsatile release of GnRH. This inhibition stops at puberty.

Abnormal puberty:

1) True precocious puberty:

- Early development of secondary sex characters with gametogenesis.

- Causes: inhibition of GnRH pulsatile generator or stimulation of GnRH secretion due to:

- a- Posterior hypothalamus tumors or infections.
- b- Constitutional.
- c- Pineal tumors secondary to hypothalamic damage.
- d- Gonadotropin – independent precocity:

In which, precocious gametogenesis & steroidogenesis can occur without the pubertal pattern of gonadotropin secretion.

In some cases, are caused by +++ sensitivity of LH receptors to gonadotrophins due to active mutation of G – protein that couples the receptors to adenylyl cyclase.

2) Precocious pseudopuberty:

- Early development of secondary sexual characteristics without gametogenesis (spermatogenesis or oogenesis).

- It is due to abnormal exposure of immature males to androgen or immature females to estrogen.

- Source of sex hormones: gonadal or adrenal tumour.

3) Delayed puberty:

- Delayed menarche to 17 years & testicular development to 20 years.

- Causes: panhypopituitarism or Turner's syndrome.

- Normal gonads with normal endocrine function can be associated by delayed puberty (in males, it is eunuchoidism & in females, it is primary amenorrhea).